

Benzo[a]pyrene

- 1924 Classical study by Kennaway demonstrated that isoprene pyrolysis yields a tar of considerable carcinogenicity to the experimental animal. Tar contained PAH whose spectra was similar to but not identical with benz[a]anthracene. [1]
- 1933 Cook *et al.* synthesized BaP and claimed that it was the major carcinogen in coal tar. This synthesis led to chemical analytical studies with polynuclear aromatic hydrocarbons and was considered a milestone in chemical carcinogenesis. [2]
- 1939 Roffo isolated benzo[a]pyrene from tobacco tar produced by pyrolysis. [3]
- 1947 Berenblum and Shubik, in their studies of cocarcinogenesis, described the potentiating effect of croton oil (which in itself is almost always non-carcinogenic) on the action of the hydrocarbon carcinogen benzo[a]pyrene. [4]
- 1953 A group of investigators, headed by Lindsey, was first to succeed in the identification of polynuclear aromatic hydrocarbons in tobacco smoke; presence of benzo[a]pyrene in chromatography and fractions was confirmed also by fluorescence spectra. [5]
- 1954 Cooper, Lindsey and Waller reported 1 microgram of benzo[a]pyrene through use of absorption spectrophotometry and the fluorescence spectrography. [6]
- 1955 Seelkopf reported presence of benzo[a]pyrene in cigarette "tar". [7]

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- 1955 Lam reported benzo[a]pyrene through spectrophotometry of pyrolysate of aliphatic hydrocarbons from cigarette butts. [8]
- 1955 Wynder and Wright estimated that there can be no more than one part per million of benzo[a]pyrene in the total condensate. They state that "... the concentration in which benzo[a]pyrene seems to be in cigarette tar is insufficient to account for the observed carcinogenic activity to mouse epidermis." [9]
- 1955 Stocks and Campbell calculated the amount of BaP inspired per year by a resident in an urban, a mixed, and a rural area of England. The values obtained were 450, 157 and 41 micrograms respectively. Contrast these values with the amount taken in by a pack-a-day inhaling smoker; for example, 146 micrograms per year (using a value of 2 micrograms in the mainstream smoke of 100 cigarettes). [10]
- 1956 Cardon *et al.* published the first U. S. report of benzo[a]pyrene. [11]
- 1956 Lyons reported 7.4 micrograms of benzo[a]pyrene in mainstream smoke from 500 cigarettes, through fluorescent spectrography and absorption spectrophotometry. [12]
- 1956 Wynder and Wright reported benzo[a]pyrene to be present in neutral cigarette smoke condensate by spectrographic analysis. They stated, " ... only the paper burned unrealistically in bulk shows the presence of benzo[a]pyrene above the detectable level [1 to 10 ppm]." (emphasis added) [13]
- 1956 Kuratsune explored the presence of benzo[a]pyrene in various materials and found none in cigarette smoke. Some was found in cigarette ends and ashes; the resulting conclusion: " ... small amounts of benzpyrene are produced by smoking, but then only a very small

part ... thus formed appears in the inhaled smoke."
[14]

- 1956 Wright described experiments showing that cigarette paper burned in a manner much like the cylindrical form of a cigarette did not yield benzo[a]pyrene. Only paper burned in bulk yielded that particular compound. [15]
- 1957 Citing investigators of carcinogens in tobacco tar (Cooper and Lindsey, Lyons, Latarjet, etc.), Wynder and Wright state, "[W]e have demonstrated experimentally ... that, 0.0001 per cent or even 0.0005 per cent benzpyrene in acetone will not produce any tumors on the present experimental mouse or rabbit groups. Thus there is conclusive proof that the animal results cannot be solely due to the benzpyrene content of tobacco."
- According to Wynder and Wright "... the benzpyrene content of the total tar as well as of the active fractions is far too low to account alone for the positive [animal] results. So far, no carcinogens have been identified in large enough quantity in tobacco tar or its fractions to account for the observed activity." [16]
- 1958 Van Duuren found benzo[a]pyrene to have strong carcinogenic potential in his experiments with the aromatic hydrocarbons in cigarette mainstream smoke. However, he concludes that "the carcinogenic hydrocarbons found so far do not by themselves appear to be present in sufficient concentrations to account for the observed activity." [17]
- 1958 Bailey found as much benzo[a]pyrene in one kilogram of smoked trout and mutton as in the smoke from 350 cigarettes. [18]
- 1958 Gellhorn reported that condensates of cigarette smoke have cocarcinogenic or promoting properties. He found that the application of a mixture of

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benzo[a]pyrene plus condensates of cigarette smoke to mouse skin resulted in neoplastic changes, whereas the same concentration of benzo[a]pyrene alone failed to elicit tumors. [19]

- 1959 Hoffmann and Wynder isolated crystalline benzo[a]pyrene from cigarette mainstream smoke; their data supported previous data showing benzo[a]pyrene to be a potent carcinogen to mouse skin. [20]
- 1959 Wynder notes that many have identified benzo[a]pyrene in tobacco smoke but " ... it is generally realized, of course, that this amount of benzpyrene is not sufficient to account by itself for the carcinogenic activity of the total tar." [21]
- 1961 The production of lung tumors following intratracheal administration of benzo[a]pyrene was first demonstrated by Ryazanov *et al.* in a study in which one or five administrations of 100 milligrams benzo[a]pyrene to eight rats produced at least three lung tumors. [22]
- 1961 According to Burney, in citing U.S. Public Health Service surveys, the mainstream smoke from 1 pack of cigarettes per day would contribute about 60 micrograms of benzo[a]pyrene per year. A person inhaling the air in some cities would take in from 110 to 150 micrograms per year. [23]
- 1961 Druckrey performed experiments with benzo[a]pyrene and found that the amounts present in mainstream smoke condensates cannot account for more than a few percent of the activity of tobacco products. [24]
- 1962 Roe conducted a study investigating the role of benzo[a]pyrene as a possible initiator in the carcinogenic effect of mainstream cigarette smoke toward mice. After experimenting with

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benzo[a]pyrene and smoke condensate at various levels it was shown that the benzo[a]pyrene content of cigarette smoke could be increased 10 times without a significant increase in the yield of tumors. These results indicate that benzo[a]pyrene is not necessarily of primary importance in the initiation of tumors by cigarette smoke. [25]

- 1964 The report of the Advisory Committee to the U.S. Surgeon General found benzo[a]pyrene "one of the most potent of all the carcinogens now known," and further stated that, along with dibenzo[a,i]pyrene "benzo[a]pyrene is one of the two most potent of the seven carcinogens detected in tobacco smoke and it is present in much larger quantity than any of the other carcinogens listed." [26]
- 1965 Wynder and Hoffmann, in categorizing tumorigenic agents which might be present in cigarette mainstream smoke, suggested assigning benzo[a]pyrene as an indicator for tumor-initiation in aromatic hydrocarbons. [27]
- 1966 Lazar *et al.*, in a thorough study of benzo[a]pyrene, reported that increasing the benzo[a]pyrene content of cigarette mainstream smoke by as much as 30 times gave no increase of carcinogenic activity on mouse epidermis. They concluded that the "benzo[a]pyrene content is not important in the carcinogenicity of cigarette smoke condensate." [28]
- 1967 Wynder and Hoffmann reported that the benzo[a]pyrene content per milligram of "tar" had dropped over the years as cigarette designers incorporated various factors., e.g., stem sheet. (This trend has continued with the introduction of porous paper and expanded tobacco). [29]
- 1969 Rathkamp and Hoffmann demonstrated that nitrates added to tobacco decreased levels of carcinogenic PAH

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in smoke (and also the mouse-skin tumorigenicity). Later studies indicated that increased nitrate resulted in an increased nitrosamine content. [30]

- 1969 Hammond, Selikoff and Lawther conducted a study involving male members of the roofers' union and their high level of exposure to benzo[a]pyrene. The researchers estimated that in one day a nonsmoking roofer might inhale the amount of BaP contained in 715 cigarettes. Even if all the men studied had been nonsmokers (which they were not) and worked only one day a week, "they still would have inhaled at least as much BaP per year as very heavy cigarette smokers in the general population." If this hypothesis were true their death rate "should have been at least two or three times as high as the lung cancer death rate of all men in the U.S. We conclude that if a high level of exposure to benzo[a]pyrene has any effect in relation to lung cancer, the effect must be small [I]f a high level of occupational exposure to benzo[a]pyrene by way of inhalation results in little if any increase in the risk of lung cancer - then it seems unlikely that the extremely small amount of benzo[a]pyrene in cigarette smoking can account for the high degree of association between cigarette smoking and lung cancer." [31]
- 1969 In response to the Hammond, Selikoff and Lawther study, a news release of the American Cancer Society stated "[a] known cancer causing agent in experimental animals may have to be ruled out as a cause of lung cancer in man..." [32]
- 1970 Dontenwill and co-workers reported that frequency of metastases was lower in mice treated with condensate than with benzo[a]pyrene. [33]
- 1971 Van Duuren *et al.* tested numerous tobacco-leaf and tobacco-smoke components for co-carcinogenic activity on mouse epidermis by simultaneous and repeated application with benzo[a]pyrene. Various tumor-

promoting substances were also tested, showing varied results, from co-carcinogenic activity to weak to no activity. These results indicate the complexity of the problems encountered in experimental tobacco carcinogenesis. [34]

- 1971 Krasnyanskaya examined the effects of chronic exposure of cigarette smoke on the respiratory tract of 95 rabbits. One group was pretreated intratracheally with benzo[a]pyrene. Though premalignant changes were found in treated animals, no malignancies were observed after a four year exposure. [35]
- 1972 Sydnor *et al.* reported tumor-induction experiments using an aqueous extract of cigarette smoke condensate prepared from a commercial cigarette brand together with a similar benzo[a]pyrene solution. [36]
- 1977 The Royal College of Physicians characterizes polycyclic aromatic hydrocarbons as one of the two (along with *N*-nitroso compounds) chief initiators of cancer in tobacco smoke. [37]
- 1979 The U.S. Surgeon General reported that the "levels of carcinogenic polynuclear aromatic hydrocarbons in tobacco smoke are well below their practical threshold as complete mouse skin carcinogens, but their role in tobacco smoke condensate is definitely that of a tumor initiator." Benzo[a]pyrene was categorized as a "complete carcinogen." [38]
- 1979 In two separate studies, Rinkus *et al.* (1979) and Bartsch *et al.* (1980) found several cigarette smoke constituents to be mutagenic. Among those was BaP. [39]
- 1980
- 1982 The Report of the U. S. Surgeon General classifies benzo[a]pyrene as a "toxic and tumorigenic agent" of

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cigarette smoke with amounts of 8-40 nanograms per cigarette. [40]

- 1985 The International Agency for Research on Cancer, in a review of the polynuclear aromatic hydrocarbons in tobacco smoke and their potential carcinogenic activity found sufficient evidence to consider benzo[a]pyrene carcinogenic to experimental animals. They report levels of 0.8 micrograms per gram in Maryland and burley tobacco, 1.1 micrograms per gram in oriental tobacco and 1.4 microgram per gram in flue-cured tobacco. [41]

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